SCIENTIFIC LETTER

β blocker treatment is associated with improvement in renal function and anaemia in patients with heart failure

W Khan, S M Deepak, T Coppinger, C Waywell, A Borg, L Harper, S G Williams, N H Brooks

Heart 2006;**92**:1856–1857. doi: 10.1136/hrt.2005.083998

Over the past three decades, there has been rapid progress in the diagnosis and management of patients with chronic congestive heart failure (CHF). However, the mortality from CHF remains high, partly due to comorbidity, the very existence of which may have excluded some patients from previous large-scale clinical trials. Hence, the full effect of modern treatment on non-trial ''real life'' patients with CHF in clinical practice remains uncertain.

Chronic renal impairment (CRI) and anaemia are common comorbidities associated with CHF, and are both independent predictors of poor prognosis.[1] It has previously been shown that treatment with either angiotensin-converting enzyme inhibitors (ACEI) or β blockers improves prognosis in patients with CHF with or without CRI.[2 3] Among the most recent treatments of CHF, ACEIs are potentially nephrotoxic and may cause worsening of anaemia.[3] Thus, the relationship between treatment and outcome in patients with CHF with CRI and anaemia needs further investigation. We aimed to assess the effect of β blocker treatment on renal function and anaemia in consecutive ambulatory patients with CHF in routine clinical practice.

METHODS

A retrospective case study of 134 consecutive patients (alive at the time of analysis) with stable CHF, attending our heart failure clinic between 2002 and 2004, was conducted. Serum creatinine and haemoglobin levels checked during 12 months before and 12 months after the initiation of β blocker treatment were recorded. Patients included in this study were clinically stable and had no history of hospital admission 6 weeks before blood testing, and had a left ventricular ejection fraction (LVEF) <45%. Patients with anaemia due to an alternate cause or those undergoing treatment for anaemia were excluded from the study. All patients had normal mean corpuscular and packed cell volumes. CRI was considered to be present when serum creatinine concentration was ⩾120 μmol/l, and anaemia if serum haemoglobin concentration was ⩽13.0 g/dl. Creatinine clearance was calculated by the Cockcroft–Gault formula.

The study was approved by the South Manchester University Hospitals Trust ethics committee and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Data are expressed as mean (standard deviation (SD)). Changes in Hb (ΔHb) and creatinine clearance (ΔCr) after β blocker treatment (and in the control group) are presented and between-group testing was carried out using the unpaired Student's t test; p values <0.05 were considered significant.

RESULTS

Table 1 shows baseline characteristics of the study population. Of the 134 patients, 106 (79%) were men, mean (SD) age 68.76 (10.54) years, range 41–88 years, mean LVEF 31.54% (8.81%), NYHA classes ranged between I (7%), II (66%) and III (9%). In all, 119 patients (93 (78%) men, mean age 68.29 (10.54) years; range 42–88 years) were treated with β blockers; 15 patients (10 men (67%), mean age 72.5 (9.68) years; range 50–87 years) had contraindications to, or could not tolerate, β blocker treatment. These patients served as the control arm of this study.

Among the 119 patients in the β blocker treatment group, 55 (46%) had CRI (46 (82%) men) and 42 (35%) were anaemic (31 (72%) men). A total of 23 (19%) patients had both CRI and anaemia. Among the 15 patients in the control group, 10 (66%) had CRI, and 8 (53%) had both CRI and anaemia. In patients who were receiving β blocker treatment, there was a significant 8.1% increase in creatinine clearance (mean (SD), Δ 3.4 (9.0) ml/min). In the control group, there was a significant 17.7% reduction in creatinine clearance (Δ −8.3 (10.6) ml/min; p<0.001; ΔCr, β blocker group *v* control). The 42 patients with anaemia also favourably responded to (β blocker treatment, with a significant 6.7% increase in mean haemoglobin levels (Δ 0.86 (1.3) g/dl; p<0.001). In the eight patients with anaemia in the control group, there was a significant 15.4% reduction in Hb (Δ −2.0 (2.0) g/dl; p<0.001; ΔHb, (β blocker group *v* control).

Table 1 Baseline characteristics of study population

Age, years	68.7 (10.5)
Male, n (%)	106 (79)
CHF duration since diagnosis, months	33.9 (46)
NYHA class I/II/III (%)	7/66/9
LVEF, %	31.5±8.8
Aetiology and risk factors, n (%)	
Ischaemic heart disease	79 (58.9)
Hypertensive heart disease	35 (26)
Valvular heart disease	26 (19)
Atrial fibrillation	17 (12.6)
Alcoholic cardiomyopathy	10 (7)
Diabetes	26 (19.4)
Hyperlipidaemia	34 (25)
Smoking history	67 (50)
Concomitant treatment, n (%)	
ACEI	
Angiotensin II receptor antagonists	12 (8)
Diuretics	115 (85)
Statins	92 (68)
β blockers	119 (89)

ACEI, angiotensin-converting enzyme inhibitor; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Values are expressed as mean (SD) or n (%).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; CHF, congestive heart failure; CRI, chronic renal impairment; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction

DISCUSSION

Chronic renal impairment and anaemia are common important comorbidities in patients with CHF, and are both independent prognostic indicators.[1] In our study, nearly 50% of the study population had CRI, and anaemia was found in >30%. Moreover, 55% of patients with anaemia also had CRI. We observed that in patients who were treated with β blockers, both CRI and anaemia improved.

The mechanism of CRI in CHF is not fully understood. Glomerular filtration rate (GFR) is dependent on renal perfusion pressure, which is mainly dependent on cardiac output.[4] As the renal blood flow is affected proportionally more than cardiac output in CHF, the renal haemodynamic reserve is already diminished at an early stage of left ventricular dysfunction. An increase in the filtration fraction maintains an adequate GFR at this early stage.[5] It has been suggested that a low renal plasma flow is one of the characteristic mechanisms of CRI in patients with CHF.[6] β blocker treatment-related improvement in cardiac output and renal perfusion pressure may be one of the mechanisms of improvement in renal function seen in our study population.

Several factors contribute to anaemia in patients with CHF. The activation of renin–angiotensin–aldosterone and vasopressin systems leads to salt and water retention. This results in haemodilution and ''pseudoanaemia'', which has a worse prognosis than ''true'' anaemia.[7] Factors closely related to anaemia of chronic disease are poor utilisation of apparently adequate iron stores, cytokine activation and impaired synthesis of erythropoietin. Like other chronic disease states, inflammatory cytokines are raised in patients with CHF or CRI and play an important part in causing anaemia due to impaired renal synthesis of erythropoietin and defective supply of iron for erythropoiesis.[7] Recent studies have shown that β blockers have an anti-inflammatory effect and that treatment with β blockers is associated with changes in CRP levels.[8] We, therefore, hypothesise that an improvement in anaemia, seen in our study patients, resulted from a combined effect of β blocker treatment on renal function (by an improvement in creatinine clearance) and their anti-inflammatory effects, which resulted in restoring renal erythropoietin generation and improved peripheral action of erythropoietin. Those patients who had contraindications to β blocker treatment tended to develop CRI and anaemia during the course of progressive CHF.

This study has shown that β blocker treatment is associated with an improvement in CRI and anaemia. Further large-scale studies are needed to confirm our findings and to investigate the underlying mechanisms.

Authors' affiliations

W Khan, S M Deepak, T Coppinger, C Waywell, A Borg, L Harper, S G Williams, N H Brooks, Heart Failure Unit, North West Regional Cardiac Centre, South Manchester University Hospital, Manchester, UK

Competing interests: None declared.

Correspondence to: S Williams, Heart Failure Unit, South Manchester University Hospitals Trust, Wythenshawe, Manchester M23 9LT, UK; simongwilliams@hotmail.co.uk

Accepted 7 May 2006

REFERENCES

1 **McClellan WM**, Flanders WD, Langston RD, *et al*. Anaemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population based study. *J Am Col Nephrol* 2002;**44**:63–7.
2 **Erdmann E**, Lechat P, Verkenne P, *et al*. Results from post-hoc analysis of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *Eur J Heart Failure* 2001;**3**:469–79.
3 **Marathias KP**, Agroyannis B, Mavromoustakos T, *et al*. Hematocrit-lowering effect following inactivation of renin-angiotensin system with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Curr Top Med Chem* 2004;**4**:483–6.
4 **Hillege HL**, Girbes ARJ, de Kam PJ, *et al*. Renal function, neurohormonal activation, and survival in patients with chronic renal function. *Circulation* 2000;**102**:203–10.
5 **Ljungman S**, Laragh, JH, Cody RJ. Role of the kidney in congestive heart failure. Relationship of cardiac index to kidney function. *Drugs* 1990;**39**(Suppl 4):10–24.
6 **Leithe ME**, Margorien RD, Hermiller JB, *et al*. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. *Circulation* 1984;**69**:57–64.
7 **Opasich C**, Cazzola M, Scelsi L, *et al*. Blunted erythropoietin production and defective iron supply for erythropoeisis as major causes of anaemia in patients with chronic heart failure. *Eur Heart J* 2005;**26**:2232–7.
8 **Jenkins NP**, Keevil BG, Hutchinson IV, *et al*. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. *Am J Med* 2002;**112**:269–74.